PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 May 2001 (15.05.01)	
International application No. PCT/GB00/02864	**Applicant's or agent's file reference** SMC 60378/WO
International filing date (day/month/year) 25 July 2000 (25.07.00)	**Priority date** (day/month/year) 03 September 1999 (03.09.99)
Applicant COLLINS, Andrew, Neale et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

26 February 2001 (26.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SMC 60378/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02864	25/07/2000	03/09/1999
International Patent Classification (IPC) or national classification and IPC A01N47/44		
Applicant AVECIA LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26/02/2001	22.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich T l. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Mitchell, G Telephone No. +49 89 2399 8678

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02864

I. Basis of th r port

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-27 as originally filed

Claims, No.:

1-23 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they hav been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-11, 13, 15, 16
	No:	Claims	1-6, 12, 14, 17-23
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations
see separate sheet

R Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The present application relates to antimicrobial polymers which carry a chromophoric marker (claims 1-16), a composition comprising said antimicrobial polymers (claims 18 and 19), a method for inhibiting microorganism growth (claim 20), a method for detecting antimicrobial polymer (claims 21 and 22), a method of maintaining the concentration of the antimicrobial polymer (claim 23) and a compound of the formula 2 which is used as a chromophore marker carrying the reactive functional group (claim 17).

The following documents (D) are cited from the International Search Report:

D1: DATABASE WPI Section Ch, Week 197924 Derwent Publications Ltd., London, GB; Class A14, AN 1979-45362B XP002151861 & SU 619 489 A (AS USSR MICROMUL CP), 4 July 1978 (1978-07-04)
D2: WO 98 02492 A
D3: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN-INTERNATIONAL, accession no. 1982:190473 XP002151859 & JP 56 167383 A 23 December 1981 (1981-12-23)
D4: US-A-5 235 045
D5: US-A-5 498 547

D1 discloses the modification of N-vinyl pyrrolidonecrotonaldehyde and N-vinyl pyrrolidone-maleic anhydride copolymers with luminescent amino derivatives of acridine.
The aim of D2 is to modify polymers with a highly fluorescent dye, so that the dye becomes a part of the molecule such that the polymer can be readily detected in the ppb range (page 2, line 11-16). D2 relates specifically to Rhodamine B which is incorporated covalently into a polymer such as diallyldimethylammonium chloride. The polymers of D2 are used in water treating applications. The dosage and residual quantities of the polymers can be controlled and monitored using conventional fluorescence detecting equipment (page 3, line 5-12).

D3 discloses dye laser naphthalimides. D4 relates to the synthesis of several 3-bromo-4-alkylamino-N-alkyl-1,8-naphthalimides and D5 also relates to a range of non-azo N-substituted 1, 8-napthalimide compounds (figure 1a-1ccc).

In light of the disclosures of the prior art, claims 1-6, 12, 14, 17 and 18-23 are not new: All possible combinations of chromophores and polymers which have antimicrobial activity, such as those disclosed in D1 and D2, fall under the general formulation of claim 1 and the dependent claims 2-6 and 12 are implicitly disclosed. D2 also destroys the novelty of claims 18-23 and compound claim 17 is rendered not novel by the disclosures of D3-D5.

However, the novelty of antimicrobial polymers which incorporate biguanide (formulae 3, 4 and 5) or bisdicyandiamide i.e. claims 7-11, 13, 15 and 16 is presently acknowledged (Art. 33(2) PCT).

The technical problem of the present application is the provision of antimicrobial polymers which carry a chromophoric marker. Use of markers is made in order that the concentration of the antimicrobial in various media can be controlled.
D2 clearly anticipates the solution of the technical problem posed in the present application, although solving it using a different marker, the suggestion for one skilled in the art to try other markers is strong. In the absence of any surprising technical effect, no inventive step can presently be acknowledged (Art. 33(3) PCT).

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
INTELLECTUAL PROPERTY GROUP
AVECIA LIMITED
Attn. REVELL, Christopher
P.O.Box 42,Hexagon House
Blackley
Manchester M9 8ZS
UNITED KINGDOM

Date of mailing *(day/month/year)* 16/11/2000	
Applicant's or agent's file reference SMC 60378/WO	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/GB 00/ 02864	International filing date *(day/month/year)* 25/07/2000
Applicant AVECIA LIMITED	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

DATE 17/11/00 GT

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Jaap Hurenkamp

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
SMC 60378/WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 02864	25/07/2000	03/09/1999
Applicant		
AVECIA LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

International Application No
PCT/GB 00/02864

A. CLASSIFICATION OF SUBJECT MATT[redacted]
IPC 7 A01N47/44 A0[redacted]/12 C09B57/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01N C09B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 197924 Derwent Publications Ltd., London, GB; Class A14, AN 1979-45362B XP002151861 & SU 619 489 A (AS USSR MICROMUL CP), 4 July 1978 (1978-07-04) abstract ---	1,3-5, 12,18,20
X	WO 98 02492 A (NALCO CHEMICAL CO) 22 January 1998 (1998-01-22) page 1, paragraph 1 page 2, paragraph 2 -page 3, paragraph 2 ---	1-6,12, 18-23

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 November 2000	16/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lamers, W

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSID[redacted]TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN-INTERNATIONAL, accession no. 1982:190473 XP002151859 abstract "IT" & JP 56 167383 A 23 December 1981 (1981-12-23)	17
X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; S.C.CHANG ET AL.: "4-Alkylamino-3-bromo-N-alkyl-1,8-naphthal imides: new photochemically activatible antiviral compounds" retrieved from STN-INTRNATIONAL, accession no. 1994:244616 XP002151860 abstract "IT" & BIOORG. MED. CHEM. LETT., vol. 3, no. 4, 1993, pages 555-556,	17
X	US 5 235 045 A (MATTHEWS J LESTER ET AL) 10 August 1993 (1993-08-10) figures 1U,1V,,1Z,1AA,1BB,1EE,	17
A	US 5 498 547 A (BLAKE KENNETH A ET AL) 12 March 1996 (1996-03-12) column 1, line 12 - line 48 column 2, line 20 - line 51	1-23
A	WO 94 09357 A (LAUFENBERG ALFRED ;MUELLER KIRSCHBAUM THOMAS (DE); WERNER BUSSE AL) 28 April 1994 (1994-04-28) page 1, paragraph 1 page 6, paragraphs 2,3 page 9, paragraph 3	1-23
A	WO 94 09360 A (SHARMAN DENNIS FRANK ;HILL MARTYN WILLIAM (GB); CTS BIOCIDES LTD () 28 April 1994 (1994-04-28) page 1, line 3 - line 4 page 1, line 17 page 1, line 24 - line 31	1-23

1

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
SU 619489	A	15-08-1978	NONE		
WO 9802492	A	22-01-1998	US	5772894 A	30-06-1998
			AU	718403 B	13-04-2000
			AU	3958997 A	09-02-1998
			BR	9710307 A	17-08-1999
			CA	2210556 A	17-01-1998
			EP	0912639 A	06-05-1999
			NO	990197 A	15-03-1999
			US	5998632 A	07-12-1999
			US	5808103 A	15-09-1998
JP 56167383	A	23-12-1981	JP	1498262 C	29-05-1989
			JP	63044312 B	05-09-1988
US 5235045	A	10-08-1993	AU	3924693 A	21-10-1993
			CA	2130828 A	30-09-1993
			EP	0639080 A	22-02-1995
			JP	7505366 T	15-06-1995
			WO	9318789 A	30-09-1993
			US	5420136 A	30-05-1995
			US	5565551 A	15-10-1996
US 5498547	A	12-03-1996	AU	687396 B	26-02-1998
			AU	6707494 A	21-11-1994
			CA	2160233 A	10-11-1994
			EP	0696353 A	14-02-1996
			JP	8509813 T	15-10-1996
			WO	9425856 A	10-11-1994
WO 9409357	A	28-04-1994	DE	4234466 A	14-04-1994
			EP	0664883 A	02-08-1995
			FI	951710 A	10-04-1995
			JP	8502359 T	12-03-1996
			NO	950429 A	06-02-1995
WO 9409360	A	28-04-1994	AU	5373394 A	09-05-1994

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* SMC 60378/WO

Box No. I TITLE OF INVENTION

Antimicrobial Polymer

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

Avecia Limited
Hexagon House
Blackley
Manchester M9 8ZS
United Kingdom

☐ This person is also inventor.

Telephone No.
0161 740 1460

Facsimile No.
0161 721 5801

Teleprinter No.

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

COLLINS, Andrew Neale
PO Box 42, Hexagon House
Blackley
Manchester M9 8ZS
United Kingdom

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

REVELL, Christopher
Intellectual Property Group
Avecia Limited
PO Box 42, Hexagon House
Blackley
Manchester M9 8ZS
United Kingdom

Telephone No.
0161 721 1142

Facsimile No.
0161 721 5801

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BOTHWELL, Brian David
PO Box 42, Hexagon House
Blackley
Manchester M9 8ZS
United Kingdom

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MCPHERSON, Graham John
PO Box 42, Hexagon House
Blackley
Manchester M9 8ZS
United Kingdom

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: GB

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby m[redacted]der Rule 4.9(a) *(mark the applicable check-boxes t one must be marked)*:

Regional Patent

- [X] **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [X] **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [X] **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [X] **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* . . . . . .

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [X] **AE** United Arab Emirates
- [X] **AL** Albania . . . . . .
- [X] **AM** Armenia . . . . . .
- [X] **AT** Austria . . . . . .
- [X] **AU** Australia . . . . . .
- [X] **AZ** Azerbaijan
- [X] **BA** Bosnia and Herzegovina . . . . . .
- [X] **BB** Barbados
- [X] **BG** Bulgaria . . . . . .
- [X] **BR** Brazil . . . . . .
- [X] **BY** Belarus . . . . . .
- [X] **CA** Canada
- [X] **CH and LI** Switzerland and Liechtenstein
- [X] **CN** China . . . . . .
- [X] **CR** Costa Rica . . . . . .
- [X] **CU** Cuba . . . . . .
- [X] **CZ** Czech Republic . . . . . .
- [X] **DE** Germany . . . . . .
- [X] **DK** Denmark . . . . . .
- [X] **DM** Dominica
- [X] **EE** Estonia . . . . . .
- [X] **ES** Spain . . . . . .
- [X] **FI** Finland . . . . . .
- [X] **GB** United Kingdom
- [X] **GD** Grenada
- [X] **GE** Georgia . . . . . .
- [X] **GH** Ghana . . . . . .
- [X] **GM** Gambia
- [X] **HR** Croatia . . . . . .
- [X] **HU** Hungary . . . . . .
- [X] **ID** Indonesia
- [X] **IL** Israel . . . . . .
- [X] **IN** India . . . . . .
- [X] **IS** Iceland
- [X] **JP** Japan . . . . . .
- [X] **KE** Kenya . . . . . .
- [X] **KG** Kyrgyzstan . . . . . .
- [X] **KP** Democratic People's Republic of Korea . . . . . .
- [X] **KR** Republic of Korea . . . . . .
- [X] **KZ** Kazakhstan . . . . . .
- [X] **LC** Saint Lucia
- [X] **LK** Sri Lanka .
- [X] **LR** Liberia
- [X] **LS** Lesotho . . . . . .
- [X] **LT** Lithuania
- [X] **LU** Luxembourg
- [X] **LV** Latvia
- [X] **MA** Morocco . . . . . .
- [X] **MD** Republic of Moldova . . . . . .
- [X] **MG** Madagascar . . . . . .
- [X] **MK** The former Yugoslav Republic of Macedonia . . . . . .
- [X] **MN** Mongolia
- [X] **MW** Malawi . . . . . .
- [X] **MX** Mexico . . . . . .
- [X] **NO** Norway
- [X] **NZ** New Zealand . . . . . .
- [X] **PL** Poland . . . . . .
- [X] **PT** Portugal . . . . . .
- [X] **RO** Romania
- [X] **RU** Russian Federation . . . . . .
- [X] **SD** Sudan
- [X] **SE** Sweden
- [X] **SG** Singapore
- [X] **SI** Slovenia . . . . . .
- [X] **SK** Slovakia . . . . . .
- [X] **SL** Sierra Leone . . . . . .
- [X] **TJ** Tajikistan . . . . . .
- [X] **TM** Turkmenistan . . . . . .
- [X] **TR** Turkey . . . . . .
- [X] **TT** Trinidad and Tobago . . . . . .
- [X] **TZ** United Republic of Tanzania
- [X] **UA** Ukraine . . . . . .
- [X] **UG** Uganda . . . . . .
- [X] **US** United States of America . . . . . ~~continuation-in-part~~ . . . . . .
- [X] **UZ** Uzbekistan . . . . . .
- [X] **VN** Viet Nam . . . . . .
- [X] **YU** Yugoslavia . . . . . .
- [X] **ZA** South Africa . . . . . .
- [X] **ZW** Zimbabwe . . . . . .

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- [X] DZ Algeria . . . . . X MZ Mozambique . . . . . .
- [X] AG Antigua and Barbuda . . . . . X BZ Belize . . . . . .

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

*1. If, in any of the Boxes, **the space is insufficient** to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

*(i) **if more than two persons are involved as applicants and/or inventors** and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

*(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication **"the States indicated in the Supplemental Box"** is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

*(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, **the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America**: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

*(iv) if, in addition to the agent(s) indicated in Box No. IV, there are **further agents**: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

*(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "**patent of addition**," or "**certificate of addition**," or if, in Box No. V, the name of the United States of America is accompanied by an indication "**continuation**" or "**continuation-in-part**": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

*(vi) if, in Box No. VI, there are **more than three earlier applications whose priority is claimed**: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;*

*(vii) if, in Box No. VI, **the earlier application is an ARIPO application**: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.*

*2. If, with regard to the **precautionary designation statement** contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

*3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning **non-prejudicial disclosures or exceptions to lack of novelty**: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.*

Continuation of Box IV

FAWKES, David Melville
LOCKE, Timothy John
MAYALL, John
PUGSLEY, Roger Graham
SCHMITT, Maja
SHELLER, Alan

All of Intellectual Property Group, Avecia Limited, PO Box 42, Hexagon House, Blackley, Manchester M9 8ZS, United Kingdom

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 03/09/1999 3 September 1999	9920774.8	GB		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): 1

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* :

ISA / EPO

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 05
description (excluding sequence listing part)	: 27
claims	: 04
abstract	: 01
drawings	:
sequence listing part of description	:
Total number of sheets	: 37

This international application is **accompanied by** the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: ENGLISH

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

For Avecia Limited - COLLINS, AN., BOTHWELL,BD. and MCPHERSON, GJ

REVELL, Christopher

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA /
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

REVELL, Christopher
Intellectual Property Group
Avecia Limited
PO Box 42
Hexagon House
Blackley
Manchester M9 8ZS

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	22.11.2001
Applicant's or agent's file reference: SMC 60378/WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02864	25/07/2000	03/09/1999

Applicant: AVECIA LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

DATE ENTERED INTO XEN...	DATE	INITIALS
...REMINDER		
...JOURNAL		
*** TO BE VERIFIED	YES	NO
XEN-PAT ENTRY VERIFIED		

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	DA ROCHA, O. Tel.+49 89 2399-8101

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SMC 60378/WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02864	25/07/2000	03/09/1999
International Patent Classification (IPC) or national classification and IPC A01N47/44		
Applicant AVECIA LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26/02/2001	22.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Mitchell, G Telephone No. +49 89 2399 8678

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02864

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-27 as originally filed

Claims, No.:

1-23 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , *which is:*

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-11, 13, 15, 16
	No:	Claims	1-6, 12, 14, 17-23
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations
see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The present application relates to antimicrobial polymers which carry a chromophoric marker (claims 1-16), a composition comprising said antimicrobial polymers (claims 18 and 19), a method for inhibiting microorganism growth (claim 20), a method for detecting antimicrobial polymer (claims 21 and 22), a method of maintaining the concentration of the antimicrobial polymer (claim 23) and a compound of the formula 2 which is used as a chromophore marker carrying the reactive functional group (claim 17).

The following documents (D) are cited from the International Search Report:

D1: DATABASE WPI Section Ch, Week 197924 Derwent Publications Ltd., London, GB; Class A14, AN 1979-45362B XP002151861 & SU 619 489 A (AS USSR MICROMUL CP), 4 July 1978 (1978-07-04)

D2: WO 98 02492 A

D3: DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; retrieved from STN-INTERNATIONAL, accession no. 1982:190473 XP002151859 & JP 56 167383 A 23 December 1981 (1981-12-23)

D4: US-A-5 235 045

D5: US-A-5 498 547

D1 discloses the modification of N-vinyl pyrrolidonecrotonaldehyde and N-vinyl pyrrolidone-maleic anhydride copolymers with luminescent amino derivatives of acridine.

The aim of D2 is to modify polymers with a highly fluorescent dye, so that the dye becomes a part of the molecule such that the polymer can be readily detected in the ppb range (page 2, line 11-16). D2 relates specifically to Rhodamine B which is incorporated covalently into a polymer such as diallyldimethylammonium chloride. The polymers of D2 are used in water treating applications. The dosage and residual quantities of the polymers can be controlled and monitored using conventional fluorescence detecting equipment (page 3, line 5-12).

D3 discloses dye laser naphthalimides. D4 relates to the synthesis of several 3-bromo-4-alkylamino-N-alkyl-1,8-naphthalimides and D5 also relates to a range of non-azo N-substituted 1, 8-napthalimide compounds (figure 1a-1ccc).

In light of the disclosures of the prior art, claims 1-6, 12, 14, 17 and 18-23 are not new: All possible combinations of chromophores and polymers which have antimicrobial activity, such as those disclosed in D1 and D2, fall under the general formulation of claim 1 and the dependent claims 2-6 and 12 are implicitly disclosed. D2 also destroys the novelty of claims 18-23 and compound claim 17 is rendered not novel by the disclosures of D3-D5.

However, the novelty of antimicrobial polymers which incorporate biguanide (formulae 3, 4 and 5) or bisdicyandiamide i.e. claims 7-11, 13, 15 and 16 is presently acknowledged (Art. 33(2) PCT).

The technical problem of the present application is the provision of antimicrobial polymers which carry a chromophoric marker. Use of markers is made in order that the concentration of the antimicrobial in various media can be controlled.
D2 clearly anticipates the solution of the technical problem posed in the present application, although solving it using a different marker, the suggestion for one skilled in the art to try other markers is strong. In the absence of any surprising technical effect, no inventive step can presently be acknowledged (Art. 33(3) PCT).

(12) INTERNATIONAL APP ION PUBLISHED UNDER THE PATENT C ERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 March 2001 (15.03.2001)

PCT

(10) International Publication Number
WO 01/17356 A1

(51) International Patent Classification[7]: A01N 47/44, 33/12, C09B 57/00

(21) International Application Number: PCT/GB00/02864

(22) International Filing Date: 25 July 2000 (25.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9920774.8 3 September 1999 (03.09.1999) GB

(71) Applicant *(for all designated States except US)*: **AVECIA LIMITED** [GB/GB]; Hexagon House, Blackley, Manchester M9 8ZS (GB).

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/17356 A1

(54) Title: ANTIMICROBIAL POLYMER

(57) Abstract: An antimicrobial polymer, characterised in that it carries a covalently bound chromophoric marker. The antimicrobial polymer is preferably a cationic antimicrobial polymer, especially a poly(hexamethylenebiguanide). Also claimed are compositions containing the antimicrobial polymer, a method for treating a medium using the antimicrobial polymer and a method for detecting the antimicrobial polymer in a medium.

ANTIMICROBIAL POLYMER

The present invention relates to antimicrobial polymers which carry a chromophoric marker, more particularly to cationic antimicrobial polymers carrying a covalently bound chromophoric marker and to methods for detecting the antimicrobial polymers on or in a medium.

Antimicrobial polymeric compounds are used in a wide range of media to control or eliminate micro-organisms, for example industrial media such as cooling water, metal working fluids, latices, surface coatings, and geological drilling fluids; recreational waters such as swimming pools and spas; and in personal care formulations such as soaps and cosmetics. The antimicrobial polymers are used in such media as preservatives, disinfectants, slimicides and algicides. Antimicrobial polymers, especially cationic antimicrobial polymers are particularly useful and offer a number of advantages over molecular quaternary ammonium compounds, because they are of relatively low toxicity and exhibit reduced foaming when added to a liquid medium such as water.

To prevent the proliferation of micro-organisms in or on a medium containing an antimicrobial compound it is necessary to ensure that the concentration of antimicrobial compound is sufficient to give an antimicrobial effect in the medium. However, in most media, especially swimming pools, the concentration of antimicrobial compound reduces with time through a number of mechanisms, for example adsorption; chemical break down caused by interaction of the antimicrobial compound with micro-organisms or with other components present in the medium; and in the case of recirculating water systems such as swimming pools and spas by dilution when fresh water is added to the system. This can result in loss of the antimicrobial protection provided by the antimicrobial compound and the subsequent proliferation of micro-organisms.

To ensure that a medium remains protected by the antimicrobial compound it is therefore important that the concentration of antimicrobial compound in, or on, a medium can be accurately determined to ensure that sufficient concentration of the antimicrobial compound is maintained. Antimicrobial compounds are typically used at very low concentrations, often less than 10 ppm. Therefore, the system used to measure the concentration of antimicrobial compound must be able to detect ppm levels of the compound, otherwise inaccurate readings will be obtained leading to incorrect dosage levels of the antimicrobial material.

In some applications there is a need to detect the presence of the antimicrobial compound at even lower levels. For example antimicrobial compounds are often used to protect fruit against microbial degradation during storage and transportation. However, before the fruit is sold to consumers it is necessary to wash the fruit to remove the antimicrobial compounds from the fruit. Typically the washing process is required to

reduce the concentration of the antimicrobial compounds to about 1 to 10 ppb. In this application there is a need for accurate detection of the antimicrobial compound to ensure that all or substantially all of the compound has been removed during the washing process. Such detection therefore needs to be sensitive to ppb concentrations of the antimicrobial material.

However, the polymeric nature of polymeric antimicrobial compounds makes accurate determination of the concentration difficult and time consuming. This is especially true of cationic polymeric antimicrobial compounds because the cationic groups tend to associate themselves with a surface to which they are applied. To determine the concentration of the antimicrobial compound on a surface, for example on the surface of fruit, it is necessary to extract the antimicrobial compound from the surface and analyse the extract, for example using gel permeation chromatography. However, because most antimicrobial polymers comprise a mixture of polymer chains of different lengths, this procedure often gives a misleading result of the concentration because the extraction method tends to preferentially extract the shorter polymer chains.

Furthermore, polymeric antimicrobial compounds are often used in media which contain numerous other components which can interfere with the analysis method used to estimate the concentration of the polymeric antimicrobial compound. For example, in swimming pools poly(hexamethylenebiguanide) (PHMB) is commonly used as a primary sanitizer. A known colorimetric method for estimating the PHMB in the pool is based on the interaction of PHMB with bromophenol blue or Eosin dyestuffs. However, this test also detects quaternary ammonium compounds which are often present in swimming pools and thereby gives a false measure of concentration of the PHMB.

There is therefore a need for a polymeric antimicrobial material which provides good protection against the growth of undesirable micro-organisms and which can be readily detected in or a medium to which it has been applied.

We have found that by covalently binding a chromophoric marker on, or in, an antimicrobial polymer enables the antimicrobial compounds to be detected with greater accuracy, especially at low concentration without adversely affecting the antimicrobial properties of the polymer.

According to a first aspect of the present invention there is provided an antimicrobial polymer, characterised in that it carries a covalently bound chromophoric marker (hereinafter "The Polymer").

Preferably The Polymer is a cationic antimicrobial polymer, more preferably a poly(quaternary ammonium) compound, a polymeric guanide or especially a polymeric biguanide.

The chromophoric marker comprises a chromophoric group which absorbs and/or emits radiation at wavelengths characteristic of the chromophoric group. The wavelength

of absorbtion and/or emission provides a reproducible "signature" associated with The Polymer by means of which it is possible to detect the presence of The Polymer using a suitable optical or spectroscopic detection method. This signature is preferably different from any absorption or emission bands inherent in the antimicrobial polymer which does not contain the chromophoric marker, because this enables more accurate detection of the chromophoric marker, particularly at low concentrations of The Polymer in a medium

Preferably the chromophoric group has a major absorption and/or emission band in the UV, visible or near infra red range of the electromagnetic spectrum. A suitable absorption and/or emission range is from 275 to 1500nm, preferably from 390 to 1100 nm, more preferably from 400 to 800 nm.

When the chromophoric group emits radiation, it may do so via phosphorescence or more preferably fluorescence.

Suitable chromophoric groups comprise an azo, anthraquinone, pyrroline, phthalocyanine, polymethine, aryl-carbonium, triphenodioxazine, diarylmethane, triarylmethane, anthraquinone, phthalocyanine, methine, polymethine, rhodamine, indoaniline, indophenol, stilbene, squarilium, coumarin, aminoketone, xanthene, fluorine, acridene, acridan, acridinium, quinolene, thiazole, azine, nigrosine, oxazine, thiazine, indigoid quininoid, quinacridone, lactone, pyrroline, luciforyl, indacene, benzodifuranone, indolene, or an aromatic fluorescent group or a combination of such groups.

In a preferred embodiment of the present invention the chromophoric group is a fluorescent group which emits radiation in a specific fluorescence band at a wavelength which is longer than that of the absorption band. Preferably the fluorescent group has its major absorption band of in the range of from 300 to 1500nm, more preferably 390 to 1100 nm and especially from 400 to 800 nm. Preferably the fluorescence band is from 350 to 1550nm more preferably from 400 to 800nm, especially from 430 to 600nm and more especially from 440 to 460 nm.

Preferred fluorescent groups have a quantum efficiency of at least 0.01, more preferably at least 0.1 and especially 0.5. The quantum efficiency of a fluorescent material is defined as the number of photons emitted by the fluorescent material at the peak wavelength of the emission band divided by the number of photons absorbed at the peak wavelength of the absorption band by the fluorescent material. A relatively higher quantum efficiency tends to produce a greater amount of fluorescence radiation, which is easier to distinguish from any interfering radiation that may be present. Fluorescent groups having relatively higher quantum efficiencies are generally easier to detect and can therefore be used in lower concentrations on the antimicrobial polymer.

Preferred fluorescent groups include phthalocyanine; methine; croconium; stilbene, for example 4-acetamido-4'-isothiocyanatostilbene; coumarin, for example 7-amino-4-methylcoumarin and 7-amino-4-trifluoromethylcoumarin; acridan; acridinium;

luciforyl; squarylium; indacene, for example 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene; xanthene, for example Rhodamine B, Rhodamine 6G, Rhodamine 123, Fluorocein, 5-amino-Fluorocein and 5-(4,6-dichlorotriazin-2-yl)amino-Fluorocein; and an aromatic fluorescent group.

When the fluorescent group is an aromatic fluorescent group in is preferably a fluorescent polynuclear aromatic group, such as a substituted naphthylene or substituted perylene, for example 1,8-napthalimide, 4-bromo-1,8-naphthalimide, 4-methoxy-1,8-naphthalimide, 1,5-naphthalene disulphonic acid, 2-amino-1,5-naphthalene disulphonic acid. 1,8-naphthalic anhydride, 4-bromo-1,8-naphthalic anhydride, 4-methoxy-1,8-anhydride, 1,4,5,8-naphthalenetetracarboxylic acid dianhydride or perylene and thereof.

It is especially preferred that the fluorescent group is a 1,8-naphthalimide or 1,4,5,8-naphthalenetetracarboximide, or a derivative thereof.

In another preferred embodiment, the chromophoric group is one which produces a characteristic Raman spectrum when irradiated with monochromatic light. Preferred chromophores in this embodiment are rhodamines and azo dyes, especially Rhodamine 6G.

The chromophoric marker may be covalently bound to the antimicrobial polymer as a pendant group or a terminal group on the polymer chain or, most preferably as an in-chain group in the polymer chain.

When the chromophoric marker is present as a pendant or terminal group on the polymer chain, the covalent bond between the polymer and the marker is preferably formed by means of a reactive functional group on the chromophoric marker which is capable of forming a covalent bond with the polymer and/or monomer precursors used to make the polymer.

When the chromophoric marker is incorporated into the polymer chain the chromophoric marker preferably has a plurality, preferably two reactive functional groups which are capable of forming a covalent bond with one or more of the monomers, or chain segments, used to prepare the polymer and is thereby incorporated covalently as a component in the polymer chain.

The chromophoric marker may be incorporated into The Polymer by means of, for example, an ester, ether, amide, amine, imide, carbamate, disulphide, sulphide, sulphonamide, sulphonic acid ester, ureylene, thioureylene, carbonate or urethane group.

The reactive functional group(s) carried by the chromophoric marker may be any functionality which is capable of reacting with the antimicrobial polymer or a monomer used in the preparation of the antimicrobial polymer to form a covalent bond therewith. Preferred reactive functional groups include -OH, -NHR^1, -NH-, -SH, -$COOR^1$, -COZ, -SO_2Z, epoxy, alkenyl, isocyanate, thioisocyanate, an acid anhydride group or a halogen

atom (preferably chlorine or bromine), wherein R^1 is H, optionally substituted alkyl or optionally substituted phenyl and Z is halogen (especially chlorine). Preferably R^1 is H, C_{1-6}-alkyl or phenyl. More preferably R^1 is H or C_{1-4}-alkyl.

More preferably the reactive functional group is $-NH_2$, -OH, -SH, -NCO, bromine, chlorine or -NCS. It is especially preferred that the reactive functional group is $-NH_2$, -NCO or -NCS, more especially $-NH_2$.

The reactive functional group(s) may be attached directly to the chromophoric group (i.e. as an integral part of the chromophoric group) or, more preferably, through a linker group.

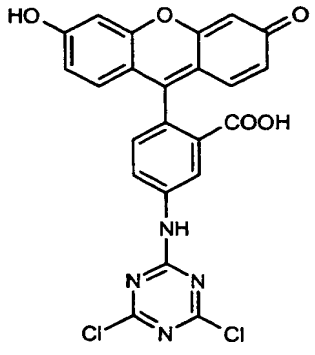
Preferred linker groups are aliphatic (preferably alkylene or alkenylene), arylene, heteroarylene or a combination thereof. When the linker group is aliphatic it preferably contains up to 10 carbon atoms. The aliphatic group may be branched but is preferably a straight chain group. Preferably the aliphatic group is a C_{1-10}-alkylene or a C_{2-10}-alkenylene group and especially a C_{2-6}-alkylene group. The aliphatic group may also contain one or more hetero atoms selected from O, S and N.

When the linker group is an arylene group it is preferably naphthylene or more preferably phenylene.

When the linker group is heteroarylene it is preferably a triazinylene or pyrimidinylene group.

When the linker group is an aliphatic, arylene or heteroarylene group it may be attached to the chromophoric group directly or, more preferably by means of a divalent atom or group. Preferred divalent atoms and groups include -O-, -S-, =N-, amide, ester, sulphonamide, carbamate, $-NR^1-$, $-NR^1C(O)NR^1-$ or $-NR^1C(S)NR^1-$, wherein R^1 is as hereinbefore defined.

The linker group may comprise a combination of the hereinbefore mentioned atoms and groups. For example the linker may comprise an alkyleneamino group wherein the amino group is attached to the chromophoric group and the alkylene group connects the amino group and the reactive functional group. By way of an example of a chromophoric marker carrying a combination of linker groups is the compound of the formula:



wherein the linker group comprises the triazinyl amino group and the reactive functional groups are the labile chlorine atoms on the traizine ring.

An especially preferred chromophoric marker which carries reactive functional group(s) is of the Formula (1):

$$Ch\text{-}\{[(T)_mL]_nX\}_p$$

Formula (1)

wherein:

Ch	is a chromophoric group;
L	is a divalent aliphatic linking group;
X	is a reactive functional group as hereinbefore defined;
T	is -O-, -S-, -NR^1-, -$NR^1C(O)NR^1$-, -$NR^1C(S)NR^1$-, -$NR^1C(O)$-, -OC(O), =N- or -SO_2NR^1-;
R^1	is as hereinbefore defined;
m and n	independently are 0 or 1; and
p	is 1 or 2.

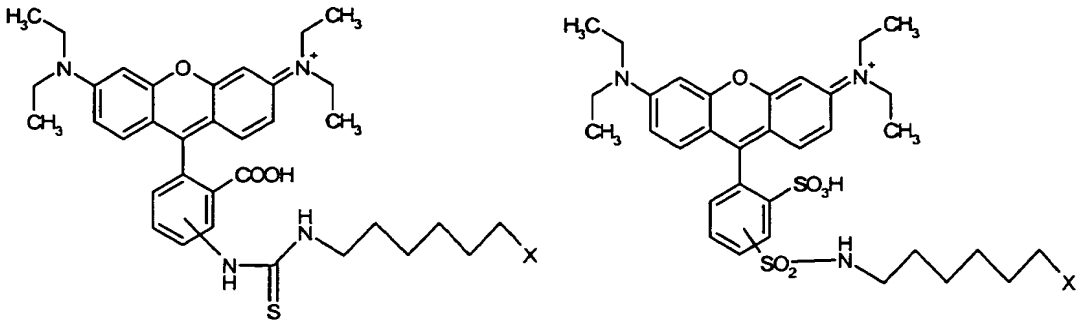
Preferably L is one of the hereinbefore mentioned aliphatic linking groups, more preferably C_{2-8}-alkylene and especially C_{2-6}-alkylene. n is preferably 1. X is preferably -OH, -NH_2 or -SH. m is preferably 1. T is preferably -NH-.

When the chromophoric marker is attached to the antimicrobial polymer as a terminal or pendant group, p is 1. When the chromophoric marker is attached as an in-chain group in the antimicrobial polymer, p is 2.

Preferred chromophoric groups represented by Ch are the hereinbefore defined preferred chromophoric groups.

Suitable mono functional chromophoric markers of the Formula (1) which carry a reactive functional group attached directly to the chromophore (i.e. those in which n and m in Formula (1) are both 0 and p is 1) include 4-acetamido-4'-isothiocyanatostilbene-2,2'-disulphonic acid, tetramethylrhodamine isothiocyanate, 1,8-naphthalic anhydride, 4-bromo-1,8-naphalthimide and N-hexyl-4-bromo-1,8-naphthalimide.

Suitable mono-functional chromophoric markers of the Formula (1) carrying a single reactive functional group attached to a chromophoric group via linking group(s) (i.e. those in which n and p are both 1 in Formula (1)) include N-(6-aminohexyl)-4-methoxy-1,8-naphthalimide and groups of the formulae:



wherein X is a reactive functional group as hereinbefore defined (for example NH_2).

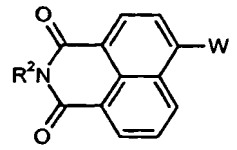
The above mentioned monofunctional chromophoric markers are suitable for use as a chain terminating or chain pendant group on the antimicrobial polymer.

Suitable bifunctional chromophoric markers of the Formula (1) carrying two reactive functional groups attached directly to a chromophoric group (i.e. those in which those in which n and m in Formula (1) are both 0 and p is 2) include 4,4'-diisothiocyanatostilbene-2,2'-disulphonic acid and 1,4,5,8-naphthalene tetracarboxylic acid dianhydride.

Suitable bifunctional chromophoric markers of the Formula (1) carrying two reactive functional groups attached to a chromophoric group via linking group(s) (i.e. those in which n is 1 and p is 2 in Formula (1)) include N-(6-aminohexyl)-4-(6-aminohexylamino)-1,8-naphthalimide and N-(6-aminohexyl)-4-methoxy-1,8-naphthalimide.

The chromophoric markers of Formula (1) may be prepared using conventional techniques, for example by condensing a compound of the formula Ch-W with the compound of the formula $H\text{-}\{[(T)_mL]_nX\}_p$, wherein W is a suitable leaving group (for example Cl) and Ch, T, L, X, m, n and p are as hereinbefore defined. Under some circumstances it may be necessary to use a suitable protecting group on the reactive functional group X to prevent it reacting with the compound Ch-W. For example, the reaction may be performed using a suitable polymer support such as a Wang resin to which the reactive group X is bound during reaction with the compound Ch-W. Following the reaction the bond with the Wang resin is cleaved, using a suitable reagent, for example an acid such as trifluoroacetic acid.

Especially preferred chromophoric markers of the Formula (1) are of the Formula (2):



Formula (2)

wherein:

W is $-NR^3R^4$, $-OR^5$ or halogen;

R^2, R^3 and R^5 are each independently, alkyl optionally substituted by a reactive functional group;

R^4 is H or alkyl optionally substituted by a reactive functional group;

provided that at least one of R^2 R^3, R^4 or R^5 is substituted by a reactive functional group.

When W is halogen it is preferably chloro or more preferably bromo. It is preferred however that W is $-OR^5$ or $-NR^3R^4$.

R^2 and R^3 are preferably C_{1-10}-alkyl, more preferably C_{1-8}-alkyl, especially C_{2-6}-alkyl and more especially hexyl substituted by a reactive functional group.

Preferably R^5 is C_{1-6}-alkyl, more preferably C_{1-4}-alkyl optionally substituted by a reactive functional group. It is especially preferred that R^5 is methyl or ethyl.

Preferred reactive functional groups which may be present on any of R^2, R^3 R^4 or R^5 are the reactive functional groups represented by X as hereinbefore defined, more preferably $-NH_2$, -SH, -NCO or -NCS and especially $-NH_2$.

R^4 is preferably H or C_{1-6}-alkyl optionally substituted by amino, hydroxy or mercapto. It is especially preferred that R^4 is H.

Especially preferred compounds of the Formula (2) include N-(6-aminohexyl)-4-(6-aminohexylamino)-1,8-naphthalimide (alternatively 2-(6-aminohexyl)-6-(6-aminohexylamino)-benzo[de]isoquinoline-1,3-dione), N-(6-aminohexyl)-4-methoxy-1,8-naphalthimide, N-(6-aminohexyl)-4-bromo-1,8-naphalthimide and N-hexyl-4-(6-aminohexyl)-1,8-naphthalimide.

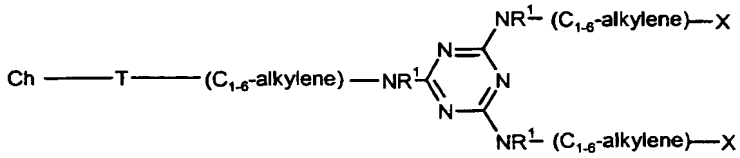
The compounds of Formula (2) are novel and form a further aspect of the present invention.

The compounds of Formula (2) may be prepared by reacting a 4-halo-1,8-naphthalic anhydride with 1 molar equivalent of a compound of the formula NH_2R^2. The reaction is preferably performed under anhydrous conditions. Optionally the reaction may be performed in a suitable inert solvent such as an ether, for example tetrahdrofuran or an alcohol, for example ethanol. The reaction is preferably performed at a temperature of from 30 to 100°C. If R^2 carries a reactive functional group it may be desirable to use a suitable protecting group or solid support to prevent the reactive functional group from reacting with the naphthalic anhydride.

When W is $-OR^5$ or $-NR^3R^4$ the product of the reaction with the naphthalic anhydride is condensed with approximately 1 molar equivalent of a compound of the

formula WH. Alternatively, when W is -OR^5 the product of the reaction with the naphthalic anhydride may be reacted with the corresponding alkoxide of the formula MOR^2, wherein M is an alkali metal such as sodium.

In another embodiment of the present invention the chromophoric marker is of the Formula (A):

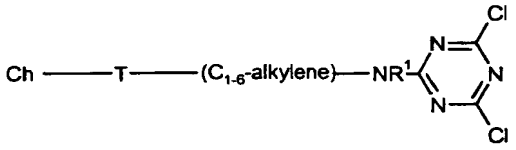


Formula (A)

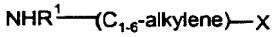
wherein:

Ch, T, each R^1 and each X^1 are, independently, as hereinbefore defined.

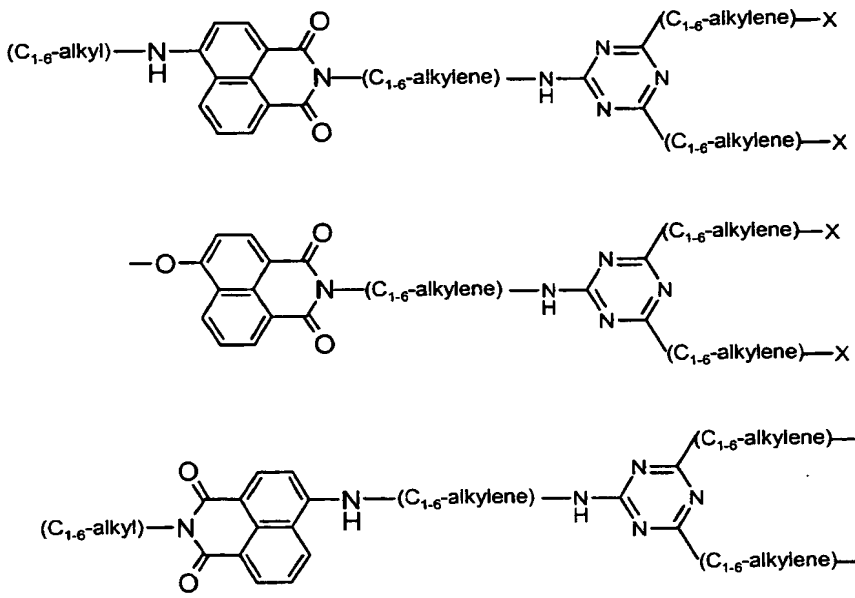
The chromophoric markers of Formula (A) may be prepared using conventional methods used in the preparation of dyes. For example a suitable technique comprises condensing the compound of the formula:



with approximately two molar equivalents of the compound of the formula:



wherein Ch, R^1,Y^1 and X^1 are as hereinbefore defined. Where appropriate the reactive functional group may be protected during the reaction as hereinbefore described for example by using a solid support such as a Wang resin. Preferred chromophoric markers of the Formula (A) are of the formulae:



wherein X is as hereinbefore defined.

Preferably the chromophoric marker is present in The Polymer at a concentration which is insufficient to significantly affect the anti-microbial properties of the polymeric material compared to a polymer without the chromophoric marker. Preferably the chromophoric marker is present at less than 10%, more preferably less than 5%, especially less than 1% based upon the total weight of The Polymer. It is especially preferred that the chromophoric marker is present at approximately 0.1% based upon the total weight of The Polymer.

As hereinbefore mentioned the chromophoric marker is covalently bound to the antimicrobial polymer. The covalent bond is preferably formed by means of reaction of one of the herein described reactive functional group with a suitable atom or group present in the antimicrobial polymer or the monomer(s) used to prepare the antimicrobial polymer. The choice of reactive functional group will depend upon the nature of the antimicrobial polymer to which it will be bound. For example, when the chromophoric marker is bound to the polymer by means of an ester group, the ester may be formed by reaction of a carboxylic acid group present on the chromophoric marker with a pendant hydroxy group on the antimicrobial polymer, or vice versa.

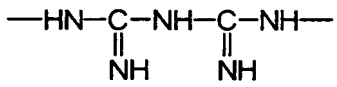
When the chromophoric marker carries an acid anhydride group, the chromophoric marker is conveniently bound to the antimicrobial polymer by means of an imide group formed by reaction of an amine group on the polymer with the acid anhydride group.

The antimicrobial polymer to which the chromophoric marker bound may be any antimicrobial polymer, preferably a cationic antimicrobial polymer, more preferably an

antimicrobial poly(quaternary ammonium) compound or a polymeric guanide and especially a polymeric biguanide.

Preferred antimicrobial poly(quaternary ammonium) compounds to which the chromophoric group is covalently bound include, for example, the ionene polymers described in US 5,866,016 cols 6 to col. 9 which are incorporated herein by reference thereto, especially poly[oxyethylene(dimethyliminio)ethylene(dimethyliminio)ethylene dichloride] (commercially available as WSCP™ from Buckman Laboratories Inc.), poly[hydroxyethylene(dimethyliminio)ethylene(dimethyliminio)methylene dichloride] and a copolymer obtainable by copolymerising 1,2-ethylenediamine, (chloromethyl)oxirane and N-methyl amine (commercially available as Busan 1157 from Buckman Laboratories Inc.).

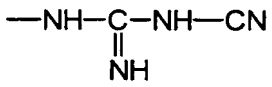
When the chromophoric marker is attached as a pendant or terminal group on a polymeric biguanide, the polymeric biguanide to which it covalently bound contains at least one biguanide unit of Formula (3):



Formula (3)

Preferably, the polymeric biguanide contains at least two biguanide units of Formula (3) which are linked by a bridging group which contains at least one methylene group. The bridging group may include a polymethylene chain which may optionally be interrupted by hetero atoms such as oxygen, sulphur or nitrogen. The bridging group may include one or more cyclic nuclei which may be saturated or unsaturated. Preferably, the bridging group is such that there are at least three, and especially at least four, carbon atoms directly interposed between two adjacent biguanide units of Formula (3). Preferably, there are not greater than ten and especially not greater than eight carbon atoms interposed between two adjacent biguanide units of Formula (3).

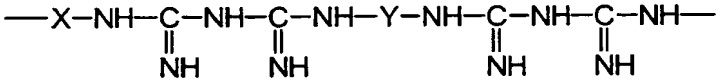
The polymeric biguanide may be terminated by any suitable group which may be a hydrocarbyl or substituted hydrocarbyl group or an amine or a group.



When the terminating group is a hydrocarbyl group, it may be alkyl, cycloalkyl or aralkyl.

When the terminating group is a substituted hydrocarbyl group, the substituent may be any substituent that does not exhibit an undesirable adverse effect on the microbiological properties of the polymeric biguanide. Examples of such substituents or substituted hydrocarbyl groups are aryloxy, alkoxy, acyl, acyloxy, halogen and nitrile.

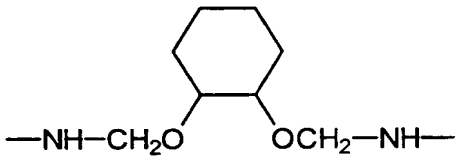
The polymeric biguanide preferably contains more than two biguanide units of Formula (3) and preferably is a linear polymeric biguanide which has a recurring polymeric unit represented by Formula (4):



Formula (4)

wherein X and Y may be the same or different and represent bridging groups in which, together, the total number of carbon atoms directly interposed between the pairs of nitrogen atoms linked by X and Y is not less than 9 and not greater than 17.

The bridging groups X and Y may consist of a polymethylene chain, optionally interrupted by a heteroatom such as oxygen, sulphur or nitrogen. X and Y may also incorporate a cyclic nucleus which may be saturated or unsaturated, wherein the number of carbon atoms directly interposed between the pairs of nitrogen atoms linked by X and Y is taken as including that segment of the cyclic group, or groups, which is the shortest. Thus, the number of carbon atoms directly interposed between the nitrogen atoms in the group



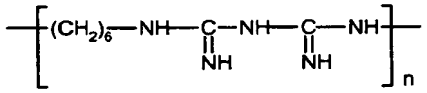
is 4 and not 8.

The preferred polymeric biguanide for use in the present invention is poly(hexamethylenebiguanide), in which both X and Y in Formula 4 are the group $-(CH_2)_6-$

The polymeric biguanides of Formula 4 are typically obtained as mixtures of polymers in which the polymer chains are of different lengths. Preferably, the number of individual biguanide units

is, together, from 3 to about 80.

In the case of the preferred poly(hexamethylenebiguanide) it is a mixture of poly(hexamethylenebiguanide) polymer chains in which the individual polymer chains, excluding the terminal groups, are represented by Formula (5) and salts thereof:

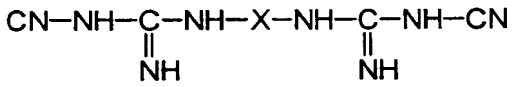


Formula (5)

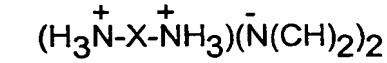
wherein the value of n is from 4 to 40 and especially from 4 to 15. It is particularly preferred that the average value of n in the mixture is 12. Preferably, the average molecular weight of the polymer mixture is from 1100 to 3300.

When the chromophoric marker is present as an in-chain group in The Polymer, The Polymer is obtainable by co-polymerising the chromophoric marker with the monomers used to prepare the antimicrobial polymer which does not contain the chromophoric marker. For example, a polymeric quaternary ammonium antimicrobial material obtainable by co-polymerising 1,2-ethlenediamine, (chloromethyl)oxirane, N-methyl amine and a chromophoric marker as hereinbefore defined.

In a preferred embodiment of the present invention The Polymer is a polymeric biguanide wherein the chromophoric marker is incorporated into the polymer chain.
In this preferred embodiment The Polymer is obtainable by the copolymerisation of a chromophoric marker, a bisdicyandiamide having the formula:



and a diamine $H_2N\text{-}Y\text{-}NH_2$, wherein X and Y have the meanings defined above. Alternatively The Polymer is obtainable by copolymerisation of a chromophoric marker, a diamine salt or dicyanimide having the formula:



and a diamine $H_2N\text{-}Y\text{-}NH_2$ wherein X and Y have the meanings defined above. These methods of preparation are analogous to those described in UK specifications numbers 702,268 and 1,152,243 respectively. Any of the polymeric biguanides described in GB 702,268 and GB 1,152,243 may be prepared with a chromophoric marker present in the polymer chain by addition of a chromophoric marker during the copolymerisation of the monomers used to prepare the polymeric biguanides described therein.

It is especially preferred that The Polymer is obtainable by co-polymerising hexamethylenediamine, hexamethylene-1,6-bis dicyandiamide (HMBDA) and a chromophoric marker.

In this preferred embodiment the chromophoric marker is preferably a compound of the Formula (2) as hereinbefore defined. It is especially preferred that the chromophoric marker of the Formula (2) is N-(6-aminohexyl)-4-(6-aminohexylamino)-1,8-naphthalimide, N-(6-aminohexyl)-4-methoxy-1,8-naphthalimide, N-(6-aminohexyl)-4-bromo-1,8-naphthalimide or N-hexyl-4-(6-aminohexyl)-1,8-naphthalimide. We have found that these chromophoric marker provide a strong fluorescent signal and the presence of the aminohexyl groups closely resemble the hexamethylene groups present in the unmarked poly(hexamethylenebiguanide) polymer, thereby minimising the effect of the

chromophoric marker on the antimicrobial properties of The Polymer compared to the unmarked antimicrobial polymer.

In another preferred embodiment The Polymer is obtainable by co-polymerising hexamethylenediamine, hexamethylene-1,6-bis dicyandiamide (HMBDA) and a 4-halo-1,8-naphthalic anhydride, especially 4-bromo-1,8-naphthalic anhydride .

It is believed that during the copolymerisation the 4-bromo-1,8-naphthoalic anhydride reacts with 2 molar equivalents of the hexamethylene diamine to give N-(6-aminohexyl)-4-(6-aminohexylamino)-1,8-naphthalimide. The 1,8-naphthalimide groups are thereby incorporated into The Polymer as an in-chain chromophoric marker. This preferred embodiment has the advantage that it enables simple incorporation of the chromophoric marker into the antimicrobial polymer without the need for additional process stages to functionalise the naphthalic anhydride with alternative reactive functional groups (such as aminohexyl groups) prior to reaction with the monomers.

In these preferred embodiments the co-polymerisation of the hexamethylenediamine, hexamethylene-1,6-bis dicyandiamide (HMBDA) and a chromophoric marker containing reactive functional groups is preferably performed at a temperature of from 80 to 200°C, more preferably 110 to 170°C and especially from 120 to 160°C. The molar ratio of HMBDA to hexamethylenediamine is preferably approximately 1:1

When The Polymer is cationic, it may be used in free base form but is preferably used in the form of a salt with an acid. Preferred salts are those with an inorganic acid, especially the hydrochloride salt, and salts with organic acids. Preferred salts with organic acids are those with organic carboxylic acids, preferably carboxylic acid with from 1 to 20, more preferably from 4 to 20 carbon atoms (excluding the carbon of the carboxyl group) and optionally one or more hydroxy substituent, for example acetate, stearate or gluconate salt.

In an embodiment of the present invention The Polymer is present in admixture with one or more antimicrobial polymers which do not contain a chromophoric marker. The Polymer may be, apart from the marker, different from the antimicrobial polymer which does not contain the chromophobic marker, but is preferably the same. Such mixture may arise during manufacture wherein the amount of the chromophoric maker relative to the antimicrobial polymer, or precursor chain segments or monomers, is less than that required to give a mixture of antimicrobial polymers wherein each polymer contains one or more chromophoric markers. Alternatively, the mixture of polymers may arise from mixing together The Polymer and an antimicrobial polymer which does not contain the antimicrobial marker. In this instance The Polymer constitutes a master batch concentrate. The amount of the chromophoric marker to antimicrobial polymer may, therefore, vary over wide limits. At one extreme, the mixture of antimicrobial polymers

contains sufficient polymers containing the chromophoric marker to allow for detection of the mixture at the ppb level and at the other extreme the mixture of polymers contains only polymers which contain the chromophoric marker group.

According to a further aspect of the invention there is provided a composition comprising antimicrobial polymers at least some of which contain a chromophoric marker.

Preferably, in this embodiment, the amount of the chromophoric marker is not greater than 10%, more preferably not greater than 1%, even more preferably not greater than 0.01% and especially not greater than 0.001%, by weight, based on the amount of antimicrobial polymers.

According to a second aspect of the present invention there is provided a composition comprising a carrier and The Polymer.

The carrier may be a solid but is preferably a liquid.

The liquid may be water, a polar organic solvent or a mixture ther eof.

When the carrier is water, the aqueous composition may also contain other adjuvants which help distribute The Polymer uniformly throughout the composition. Examples of such adjuvants are compounds which provide structure to the water to inhibit sedimentation such as alginates and gums, particularly Xanthan gum.

By the term "polar" in relation to the organic solvent is meant an organic liquid or resin capable of forming moderate to strong bonds as described in the article entitled "A Three Dimensional Approach to Solubility" by Crowley et al in Journal of Paint Technology, Vol. 38, 1966, at page 269. Such organic liquids generally have a hydrogen bonding number of 5 or more as defined in the above mentioned article.

Examples of suitable polar organic liquids are amines, ethers, especially lower alkyl ethers, organic acids, esters, ketones, glycols, alcohols and amides. Numerous specific examples of such moderately strongly hydrogen bonding liquids are given in the book entitled "Compatibility and Solubility" by Ibert Mellan (published in 1968 by Noyes Development Corporation) in Table 2.14 on pages 39-40 and these liquids all fall within the scope of the term polar organic liquid as used herein.

The Polymer and compositions according to the present invention may be used to protect various media from microbiological growth.

According to a third aspect of the invention there is provided a method for inhibiting microbiological growth on, or in a medium which comprises treating the medium with The Polymer. The Polymer can be used in any conditions in which micro-organisms grow and cause problems. Thus, the medium may be an industrial medium such as a cooling water tower liquid, paper mill liquor, metal working fluid, geological drilling lubricant, polymer emulsion, surface coating composition such as paint, varnish or lacquer. The medium to be protected can be a solid such as wood or leather and particularly solid surfaces in the health-care or food preparation industries. The solid may

also be a textile material such as cellulose, including its blends with synthetic polymers and also non-woven materials such as those used in disposable items such as nappi s, incontinence pads and feminine hygiene packs.

The Polymer and compositions thereof according to the invention may also be used in personal care formulations which are of many types and include water-in-oil and oil-in-water emulsions. Many of these personal care formulations involve applications to the skin and include, inter alia, hand lotions, foundation creams, emollient creams, facial washing creams, shaving creams, after-shave lotions, sunscreen lotions and creams, sunscreen hair protectors, after-sun lotions, antiperspirants, deodorants, hair gels, hair colorants, hair mousse, mascara, eye shadows, eye liners, lipstick, lip gloss, facial blusher, rouge, foundations and fragrances, shampoo, shampoo gel, conditioning rinse, toothpaste, mouthwash, foam bath liquid, soluble bath oil and liquid soap formulations.

Where the medium to be protected is a solid, The Polymer may be applied by any method known to the art such as spraying, dipping or coating with a composition containing The Polymer.

The Polymers according to the present invention are particularly suitable for use in recirculating recreational water systems such as swimming pools and spas.

As noted hereinbefore, the amount of The Polymer which is applied to the medium to be protected from microbiological growth may be just sufficient to inhibit such growth or it may be in excess of such amount. Preferably, the amount of The Polymer which is applied to such medium is not greater than 2% and more preferably not greater than 1% by weight of the medium. Generally, adequate protection is provided by from 1 ppm to 500 ppm, particularly 10 to 200 ppm and especially 10 to 100 ppm of The Polymer relating to the medium.

The Polymer according to the present invention may be used alone or in combination with one or more further antimicrobial compound so as to increase the antimicrobial spectrum of activity. When The Polymer is used with another antimicrobial compound the components of such a mixture preferably provide a synergistic increase in antimicrobial effectiveness compared with the individual antimicrobial compounds in the composition. Indeed, many of the following examples exhibit synergism with The Polymer.

Examples of antimicrobial compounds which may be used with The Polymer include one or more of quaternary ammonium compounds such as N,N-diethyl-N-dodecyl-N-benzylammonium chloride; N,N-dimethyl-N-octadecyl-N-(dimethylbenzyl)ammonium chloride; N,N-dimethyl-N,N-didecylammonium chloride; N,N-dimethyl-N,N-didodecylammonium chloride; N,N,N-trimethyl-N-tetradecylammonium chloride; N-benzyl-N,N-dimethyl-N-(C_{12}-C_{18}-alkyl) ammonium chloride; N-(dichlorobenzyl)-N, -N-dimethyl-N-dodecylammonium chloride; N-hexadecylpyridinium chloride; N-hexadecylpyridinium

bromide; N-hexadecyl-N,N,N-trimethylammonium bromide; N-dodecylpyridinium chloride; N-dodecylpyridinium bisulphate; N-benzyl-N-dodecyl-N,N-bis(beta-hydroxy-ethyl)ammonium chloride; N-dodecyl-N-benzyl-N,N-dimethylammonium chloride; N-benzyl-N,N-dimethyl-N-(C_{12}-C_{18}-alkyl) ammonium chloride; N-dodecyl-N,N-dimethyl-N-ethylammonium ethylsulphate; N-dodecyl-N,N-dimethyl-N-(1-naphthylmethyl)ammonium chloride; N-hexadecyl- N,N-dimethyl-N-benzylammonium chloride; N-dodecyl-N,N-dimethyl-N-benzylammonium chloride and 1-(3-chloroally)-3,5,7-triaza-1-azonia-adamantane chloride; urea derivatives such as 1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin; bis(hydroxymethyl)urea; 3-(3,4-dichlorophenyl)-1,1-dimethylurea; 3-(4-isopropylphenyl)-1,1-dimethylurea; tetrakis (hydroxymethyl)acetylene diurea; 1-(hydroxymethyl)-5 ,5-dimethylhydantion and imidazolidinylurea; amino compounds such as 1,3-bis(2-ethyl-hexyl)-5-methyl-5-aminohexahydro-pyrimidine; hexamethylenetetramine; 1,3-bis(4-aminophenoxy)propane; and 2-[(hydroxymethyl)-amino]ethanol; imidazole derivatives such as 1[2-(2,4-dichloro-phenyl)-2-(2-propenyloxy)ethyl]-1H-imidazole; 2-(methoxycarbonyl-amino)-benzimidazole; nitrile compounds such as 2-bromo-2-bromomethylglutaronitrile, 2-chloro-2-chloro-methylglutaro-nitrile; 2,4,5,6-tetra-chloroisophthaladinitrile; thiocyanate derivatives such as methylene(bis)thiocyanate; tin compounds or complexes such as tributyltinoxide, chloride, naphthoate, benzoate or 2-hydroxybenzoate; isothiazolin-3-ones such as 4,5-trimethylene-4-isothiazolin-3-one, 2-methyl-4,5-trimethylene-4-isothiazolin-3-one, 2-methylisothiazolin-3-one, 5-chloro-2-methyl-isothazolin-3-one, benzisothiazolin-3-one; 2-n-butylbenzisothiazolin-3-one; 2-n-hexylbenzisothiazolin-3-one; 2-n-octylbenzisothiazolin-3-one; 2-(2-ethylhexyl)benzisothiazolin-3-one; 2-(2-ethylbutyl)benziothazolin-3-one; 2-(2-phenylethyl)benzisothiazolin-3-one; 2-methylbenzisothiazolin-3-one, 2-octylisothiazolin-3-one, 4,5-dichloro-2-octylisothiazolin-3-one; thiazole derivatives such as 2-(thiocyanomethylthio)-benzthiazole and mercaptobenzthiazole; nitro compounds such as tris(hydroxymethyl)nitromethane; 5-bromo-5-nitro-1,3-dioxane and 2-bromo-2-nitropropane-1, 3-diol; iodine compounds such as iodo propynyl butyl carbamate and tri-iodo allyl alcohol; aldehydes and derivatives such as glutaraldehyde (pentanedial), p-chlorophenyl-3-iodopropargyl, formaldehyde and glyoxal; amides such as chloracetamide; N,N-bis(hydroxymethyl)chloracetamide; N-hydroxymethyl-chloracetamide and dithio-2,2-bis(benzmethyl amide); guanidine derivatives such as 1,6-hexamethylene-bis [5-(4-chlorophenyl)biguanide]; thiones such as 3,5-dimethyltetrahydro-1,3,5-2H-thiodiazine-2-thione; triazine derivatives such as hexahydrotriazine and 1,3,5-tri-(hydroxyethyl)-1,3,5-hexahydrotriazine, 6-chloro-2,4-diethyl-amino-s-triazine and 4-cyclopropylamino-2-methylthio-6-t-butylamino-s-triazine; oxazolidine and derivatives thereof such as bis-oxazolidine; furan and derivatives thereof such as 2,5-dihydro-2,5-dialkoxy-2,5-dialkylfuran; carboxylic acids and the salts and esters thereof such as sorbic acid and 4-

hydroxybenzoic acid and their salts and esters; phenol and derivatives thereof such as 5-chloro-2-(2,4-dichloro-phenoxy)phenol; thio-bis(4-chlorophenol) and 2-phenylphenol; sulphone derivatives such as diiodomethyl-paratolyl sulphone; 2,3,5,6-tetrachloro-4-(methylsulphonyl)pyridine and hexachlorodimethyl sulphone; thioamides such as dimethyldithiocarbamate and its metal complexes, ethylenebisdithiocarbamate and its metal complexes, 2-mercaptopyridine-N-oxide and its metal complexes, azoles such as hexaconazole, propiconazole, azoconazole, cypropconazole; the compounds of Formula (1) in EP 382 375, especially azoxystrobin and chlorphthalonil.

According to a fourth aspect of the present invention there is provided a method for detecting The Polymer comprising the steps:

subjecting a sample containing The Polymer to a detection means whereby the presence of the chromophoric marker in The Polymer generates a detection signal; and

calculating the concentration of The Polymer from the detection signal generated

Preferably the detection means comprises fluorescence spectrometry or Raman spectrometry.

Preferably the concentration of The Polymer is calculated by translating the intensity of the detection signal in step (a) into the corresponding concentration of The Polymer. The intensity of the detection signal generated will be dependant upon a number of factors including the type and configuration of the detection means and the volume of the sample used. However, irrespective of these factors the signal intensity will be proportional to the concentration of The Polymer present thus enabling calibration of the detection system using standard techniques in the art. For example using a set of calibration standards containing known concentrations of The Polymer.

In a first preferred embodiment of the present method the chromophoric marker comprises a phosphorescent or more preferably a fluorescent group and the detection means is a fluorescence spectrometer comprising:

(i) a means for irradiating the sample containing The Polymer whereby the chromophoric marker is stimulated from a lower energy level to an excited state;

(ii) a means for detecting radiation (preferably fluorescent radiation) emitted by the chromophoric marker when the marker spontaneously returns to a lower energy level; and

(iii) a means for generating a detection signal upon detection of the emitted radiation.

Preferably the means for irradiating the sample containing The Polymer comprises a source of electromagnetic radiation which emits at wavelengths within the absorbtion band of the chromophoric marker. Suitable irradiation means include a laser with a peak wavelength which is within the main absorbtion band of the chromophoric marker.

Alternatively a broad-band light source may be used, optionally in conjunction with suitable optical filters to remove undesirable wavelengths outside the absorbtion band of the chromophoric marker.

The preferred means generating a detection signal is a photodetector, for example a silicon photodiode or a charge coupled array. Preferably the photodetector is used in combination with a suitable optical filter which has a transmission band corresponding with the emission band of the chromophoric marker. This minimises the effect of stray light (for example from the irradiating means) on the photodetector, thereby increasing the detection sensitivity. Upon detection of fluorescent radiation from the chromophoric marker the photodetector generates a voltage which is proportional to the intensity of fluorescent radiation generated by the sample. The intensity of fluorescent radiation is proportional to the concentration of the chromophoric marker present in the sample. Accordingly, the concentration of The Polymer can be calculated based upon the magnitude of the voltage signal generated by the photodetector.

In a second preferred embodiment of the present method the detection means comprises a Raman spectrometer.

When monochromatic light irradiates a sample most of the light is scattered elastically with no interaction. However, a small fraction of the incident light interacts with the sample causing fluorescence and inelastic scattering known as the Raman effect. The inelastically scattered radiation contains bands characteristic of the material being irradiated and is called the Raman spectrum.

The Raman effect is very weak and is often swamped by the fluorescence effect. However, the Raman spectrum can be greatly enhanced by tuning the wavelength of the incident radiation to a chromophore in a molecule. This is called Resonance Raman (RR). The strength of the spectrum can also be greatly increased by examining a molecule on a specific silver surface. This is known as Surface Enhanced Raman Spectroscopy (SERS).

The combining of Resonance Raman with SERS gives an increase in detection sensitivity. This combined effect is called Surface Enhanced Resonance Raman Spectroscopy (SERRS). Another advantage of SERRS is that fluorescence is greatly reduced or quenched and therefore masking of the Raman Spectrum caused by fluorescence is reduced. To perform SERRS the sample of interest is mixed with a silver colloid, irradiated with a monochromatic light and the SERRS spectrum measured. The spectrum is very characteristic of the chromophore of the material examined and the strength is dependent on the concentration of material present.

Thus, in the present method the concentration of The Polymer in the sample is determined by measuring the Raman spectrum generated by the chromophoric marker

and the intensity thereof, preferably using the SERRS method as hereinbefore described. The concentration of The Polymer is then determined from the intensity of the spectrum.

An example of a suitable Raman spectrometer is disclosed in US 5,751,415 which is incorporated herein by reference thereto.

According to a fifth aspect of the present invention there is provided a method for maintaining the concentration of The Polymer according to the first aspect of the invention in a medium at or above a target concentration comprising the steps:

(a) measuring the concentration of The Polymer in the medium using the method according to the fourth aspect of the present invention;

(b) comparing the measured concentration with the target concentration; and

(c) adding a sufficient quantity of further antimicrobial polymer to the medium to maintain the concentration of The Polymer in the medium at or above the target concentration.

The medium in this aspect of the invention is preferably an aqueous medium, more preferably water from a swimming pool. The preferred methods for measuring the concentration of The Polymer in step (a) are the preferred methods hereinbefore described in relation to the fourth aspect of the present invention, and especially a method which uses fluorescence spectrometry to detect the chromophoric marker in The Polymer.

The target concentration in the present method is preferably the minimum concentration of The Polymer required to prevent antimicrobial growth in the medium. Accordingly, when The Polymer is a polymeric biguanide the target concentration will typically be from 5 to 30ppm.

Preferably steps (a) to (c) of the present process are automated such that the concentration of The Polymer present in the medium is automatically maintained at or above the target level. Automation is particularly useful for the protection of swimming pools because the concentration of antimicrobial materials in swimming pools can change quickly, for example through contamination of the swimming pool, or by dilution with fresh water.

When the present method is automated it is preferred that step (b) generates an alarm signal when the concentration measured in step (a) falls to or below the target concentration. The alarm signal is then used to activate step (c) of the method and thereby increase the concentration of The Polymer. Preferably the additional antimicrobial polymer in step (c) is added to the medium from a reservoir containing The Polymer.

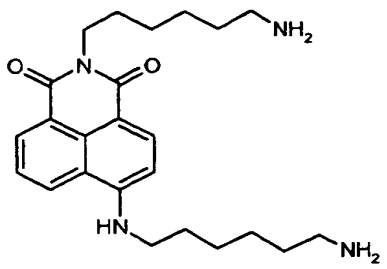
It is preferred that the concentration of The Polymer in step (a) is constantly monitored because this enables any reduction in concentration below the target level to

be quickly detected and thereby reduces the possibility of contamination of the medium through proliferation of micro-organisms in the medium.

The invention is further illustrated by the following examples in which all parts are by weight unless otherwise indicated.

Marker 1

Preparation of Chromophoric Marker N-(6-aminohexyl)-4-(6-aminohexylamino)-1,8-naphthalimide



Marker 1

Marker 1 was prepared as follows:

Stage (a) Preparation of N-acetylhexylendiamine

Hexamethylenediamine (90.64g; 0.6 mol) and acetamide (11.81g; 0.2 mol) were stirred and refluxed for 10 hours under nitrogen. The solution was cooled overnight and then distilled under vacuum <100°C as fast as possible. The N-acetylhexylenediamine was then separated from the resultant mixture by flash chromatography [SiO_2/ EtOH:25%aq.NH_3 (4:1)]. The title product was obtained as a white crystalline product (18.43g; 58% theory).

Stage (b): Preparation of N-(N-acetyl-6-aminohexyl)-4-(N-acetyl-6-aminohexylamino)-1,8-naphthalimide

4-Bromo-1,8-naphthalic anhydride (2.77g; 0.01mol) and N-acetylhexylendiamine (1.61g; 1.5 10^{-3}mol) were melted together and stirred for 1 hour until the mixture became a brown solid. The compound obtained was purified by chromatography [silica gel/ hexane, CH_2Cl_2 then CH_2Cl_2:MeOH (10:1; 5:1; 3:1)].

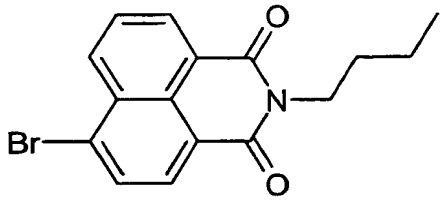
Stage (c): Preparation of N-(6-aminohexyl)-4-(6-aminohexylamino)-1,8-naphthalimide

Hydrochloric acid (250mL; 4M) was added to the product of stage (b) and the mixture was refluxed for 9 hours. The solution was cooled and neutralised with sodium carbonate. Most of the salt was precipitated with ethanol (2L), the solution filtered and the solvent evaporated. The resulting mixture was salt and a brown oil. Water (100mL)

was added and the product precipitated. The product was extracted into CH_2Cl_2 (addition of a small amount of MeOH helped dissolved the product in the CH_2Cl_2 layer), dried over MgSO4 and evaporated to give Marker 1 as an orange solid (1.90g; 46% theory).
mp: 113.6-114.9°C. Marker 1 had the following NMR spectrum:

NMR ^1H (300mHz, $CDCl_3$) δ_H: 1.1-1.6 (16H, m, $4xCH_2+4xNH_2$), 1.7-1.9 (4H, m, $4xCH_2$), 2.7 (4H, m, $2xCH_2$-NH_2), 3.4 (2H, q, Ar-N-CH_2), 4.2 (2H, t,)N-CH_2), 5.3 (1H, t, Ar-NH-R), 6.7 (1H, d, ArH), 7.6 (1H, t, ArH), 8.1 (1H, d, ArH), 8.4 (1H, d, ArH), 8.5 (1H, d, ArH) ppm
m/z (ES-): 409 $[M-H]^-$ (100%), 204 $[M-2H]^{2-}$ (15)
m/z (ES+): 411 $[M+H]^+$ (90%), 227 (100)

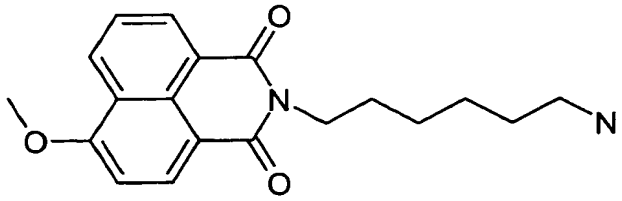
Marker 2



Marker 2

A mixture of 4-bromo-1,8-naphthalic anhydride (2.9g) and n-butylamine (0.8g) in ethanol (50ml) was stirred under reflux for 4 hours. The mixture was filtered. The residue was washed with ether and the ether solution evaporated under reduced pressure to give the title product as white solid (1.1g).
NMR ^1H (300MHz, $CDCl_3$) δ_H: 1.0 (3H, t), 1.4 (2H,m), 1.7 (2H,m), 4.15 (2H,t), 7.85 (1H,t), 8.05 (1H,d), 8.4 (1H, d), 8.55 (1H,d), 8.7 (1H) ppm

Marker 3



Marker 3

Stage 1: Coupling of hexamethylenediamine with Wang resin

Carbonyldiimidazole (12.15g) was dissolved in dichloromethane (100ml) and the solution added to Wang resin (5g of 5mmol.g-1 material) under nitrogen. The mixture was stirred at room temperature for 6 hours then allowed to stand overnight. After filtering and washing well with dichloromethane a solution of hexamethylenediamine (8.7g) in dichloromethane (50ml) was added and the mixture stirred at room temperature for 4

hours. The resin was filtered and washed well with dichloromethane. The product was air dried.

Stage 2

A mixture of the Wang resin derivative (1g) prepared in stage 1 and 4-bromo-1,8-naphthalic anhydride (1.66g) in tetrahydrofuran was stirred under reflux overnight then was cooled to room temperature. The resin was filtered, washed with tetrahydrofuran then with dichloromethane then used in the next stage.

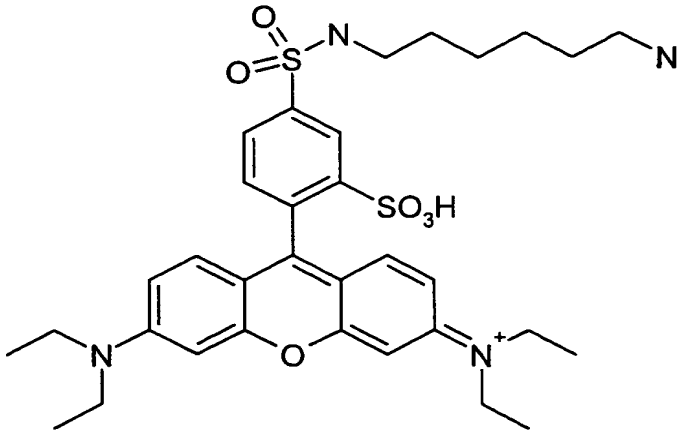
Stage 3

The product of stage 2 was stirred with a solution of trifluoroacetic acid (5ml) in dichloromethane (50ml) at room temperature for 2 hours. The mixture was filtered and washed well with dichloromethane. The combined filtrates were evaporated under reduced pressure and the resultant residue stirred with ether, filtered and air dried (0.52g).

Stage 4

A solution of sodium methoxide (0.135g) in methanol (20ml) was added to the above product and the mixture stirred under reflux overnight. After cooling to room temperature water was added and the mixture extracted with dichloromethane. The extract was washed with water, dried over magnesium sulphate and was evaporated under reduced pressure (0.2g).

Marker 4



Marker 4

Stage 1

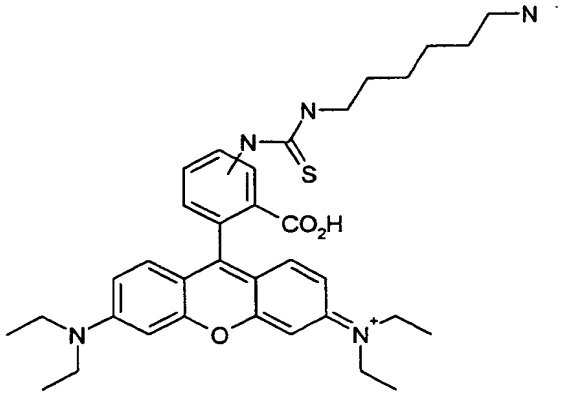
The Wang resin derivative described in stage 1 of the preparation of Marker 3 (0.33g) was suspended in dichloromethane(20ml) and triethylamine (0.1g) added,

followed by Sulforhodamine B acid chloride (0.6g). The mixture was stirred at room temperature for 4 hours, then filtered and washed with dichloromethane.

Stage 2

The above resin was stirred with a 10% solution of trifluoroacetic acid in dichloromethane (30ml) for 1 hour. Methanol was added to help dissolve the product and the mixture was filtered. The residue was washed with a mixture of dichloromethane and methanol and the combined filtrates were evaporated to dryness to give the title product, a dark red solid (0.3g).

Marker 5



Marker 5

Stage 1

The Wang resin derivative described in stage 1 of the preparation of Marker 3 (0.12g) was suspended in dichloromethane (10ml) and Rhodamine B isothiocyanate (200mg) added. The mixture was stirred at room temperature for 4 hours, then filtered and washed with dichloromethane.

Stage 2

The above resin was stirred with a 10% solution of trifluoroacetic acid in dichloromethane (20ml) for 1 hour. Methanol was added to help dissolve the product and the mixture was filtered. The residue was washed with a mixture of dichloromethane and methanol and the combined filtrates were evaporated to dryness to give a dark red solid (0.1g).

Example 1

Co-polymer containing Marker 1 as an In-Chain Group

Hexamethylenediamine dihydrochloride (1.48g; $8x10^{-3}$mol), 2% aqueous ammonium chloride solution (0.5ml), HMBDA (2g; $8x10^{-3}$mol) and Marker 1 ($3.48x10^{-3}$g)

were added to a boiling tube. The mixture was then heated at 160°C for 2 hours. The resulting product was then dissolved in water (4ml) to stop the co-polymerisation, and the temperature reduced to 70°C. More water (4ml) and Celite filter aid (0.3g) were added. The mixture was filtered and the volume made up to 15mL to give the title product as a 20% aqueous solution.

Examples 2 to 4 and Comparative Example A

Further antimicrobial polymers containing Marker 1 were prepared using the method described in Example 1, except the quantity of Marker 1 used in the co-polymerisation is as shown in Table 1. The number average molecular weight of the resulting copolymer (Mn) was measured using gel permeation chromatography. The polymer of Comparative Example A did not contain Marker 1.

Table 1

Example	% weight of Marker 1 (vs. Total weight)	Mass of Marker 1 (g)	Mn
1	0.1	$3.48\ 10^{-3}$	931.2
2	0.5	$6.96\ 10^{-3}$	841.4
3	1	$3.48\ 10^{-2}$	913.7
4	5	$6.96\ 10^{-2}$	843.0
Comparative Example A	0	0	878.3

Example 5: Co-polymer containing Marker 1 prepared in-situ

A mixture of hexamethylenediamine dihydrochloride (14.68g), HMBDA (20.05g), ammonium chloride (1.07g), 4-bromo-1,8-naphthalic anhydride (0.03g) and water (4ml) was heated at 160°C for 2 hours. Water (80ml) was added and the mixture stirred at 70°C for 1 hour. Celite filter aid was added, the solution filtered, and the volume adjusted to 150ml with water to give a 20% solution.

Examples 6 to 9 and comparative example B

PHMB polymers containing Markers 2 to 5 were prepared by a method similar to that described in Example1 except in place of Marker 1 there was used the marker shown in Table 2:

Table 2

Example	Marker	% weight of marker	Mn
6	2	0.1	1160
7	3	0.1	1190
8	4	0.1	1160
9	5	0.1	1200
Comparative example B	none	0	1190

Example 10

Anti-Microbial Effect

The Minimum Inhibitory Concentration (MIC) against a range of fungi and bacteria were determined for each of the antimicrobial copolymers prepared in Examples 1 to 4 and Comparative Example A. The MIC results are shown in Table 3:

Table 3

Example	Fungi	Bacteria						
	Ca	Pp	Bs	Ec	Psa	Sa	Ps.fl	K.pn
1	62.5	32	0.25	0.25	16	0.25	8	1
2	62.5	32	0.25	0.25	32	0.25	8	1
3	32	32	0.25	0.25	16	0.25	8	1
4	62.5	32	0.25	0.25	16	0.25	8	1
Comparative Example A	62.5	32	0.25	0.25	16	0.25	8	1
Marker 1	999	999	500	500	999	32	500	999

In Table 3 the following abbreviations are used:

Ca	*Candida albicans*	NCYC 10231
Bs	*Bacillus subtilis*	NCIB 1650
Ec	*Escherichia coli*	NCIB 9132
Psa	*Pseudomonas aeruginosa*	NCIB 10421
Sa	*Staphylococcus aureus*	NCIB 9518
Pp	*Penicillium funiculosum*	IMI 114933
Psfl	*Pseudomonas fluorescens* (with Lux AB gene)	our ref D481
Kpn	*Klebsiella pneumoniae*	ATCC 4352

Table 3 clearly shows that the presence of Marker 1 has no marked effect on the MIC compared to the polymer of Comparative Example A which does not contain Marker 1.

Table 3 also shows that Marker 1 itself has little or no antimicrobial effect compared to the copolymers containing it.

Further tests showed there was no effect on the speed of kill of Examples 1 to 4 containing Marker 1 compared to the poly(hexamethylenebiguanide) itself and which is free of Marker 1.

Example 11: Fluorescent Detection

A 20% solution of the antimicrobial polymer prepared in Example 3 (1% of Marker 1) was diluted several times with distilled water to give a range of concentrations of from 1 to $10^{-6}gL^{-1}$ of the antimicrobial polymer.

The solution containing $1gL^{-1}$ of the antimicrobial polymer was analysed by UV/Vis spectroscopy (Perkin-Elmer, Lambda 15, UV/Vis spectrometer). An absorbance peak was found at 456nm. The same analysis on a solution containing 1g/L of the polymer of Comparative Example A (no Marker 1 present) showed no peak at this wavelength.

Using a fluorescence spectrometer (Perkin-Elmer, LS-5B, luminescence spectrometer), the lambda max. excitation wavelength was found to be 452nm and the emission spectrum was scanned between 475 and 800nm. The marker maximum emission was 532nm. All the solutions were scanned and it was found that the detection limit for this particular peak was for the $10^{-6}gL^{-1}$ solution of The Polymer according to the present invention.

The above procedure was repeated using other antimicrobial polymers described in the previous Examples. The measured maximum excitation and emission wavelengths for each antimicrobial polymer is shown in Table 4.

Table 4

Antimicrobial polymer	Marker present in polymer	Concentration of marker present in polymer (% by wt)	Max. Excitation (nm)	Max. Emission (nm)
Example 6	Marker 2	0.1	454	558
Example 7	Marker 3	0.1	383,453	455,560
Example 8	Marker 4	0.1	565	593
Example 9	Marker 5	0.1	554	584

CLAIMS

1. An antimicrobial polymer, characterised in that it carries a covalently bound chromophoric marker.

2. An antimicrobial polymer according to claim 1 wherein the antimicrobial polymer is a cationic antimicrobial polymer.

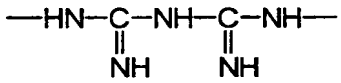
3. An antimicrobial polymer according to either claim 1 or claim 2 wherein chromophoric marker comprises a chromophoric group which has a major absorption and/or emission band in the range of from 275 to 1500 nm.

4. An antimicrobial polymer according to any one of the preceding claims wherein the chromophoric group is a fluorescent group.

5. An antimicrobial polymer according to any one of the preceding claims wherein the chromophoric marker is covalently bound to the antimicrobial polymer as a pendant group or a terminal group on the polymer chain, or as an in-chain group in the polymer chain.

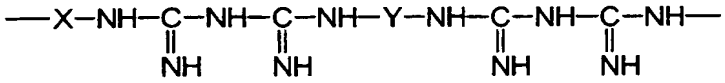
6. An antimicrobial polymer according to any one of the preceding claims wherein the chromophoric marker is present as a terminal or pendant group on the polymer chain and the antimicrobial polymer to which the chromophoric marker is bound is an antimicrobial poly(quaternary ammonium) compound, a polymeric guanide or a polymeric biguanide.

7. An antimicrobial polymer according to claim 6 wherein the antimicrobial polymer to which the chromophoric marker is bound is a polymeric biguanide which contains at least one biguanide unit of Formula (3):



Formula 3

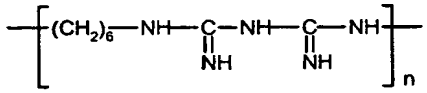
8. An antimicrobial polymer according to claim 7 wherein the polymeric biguanide is a linear polymeric biguanide which has a recurring polymeric unit represented by Formula (4):



Formula (4)

wherein X and Y may be the same or different and represent bridging groups in which, together, the total number of carbon atoms directly interposed between the pairs of nitrogen atoms linked by X and Y is not less than 9 and not greater than 17.

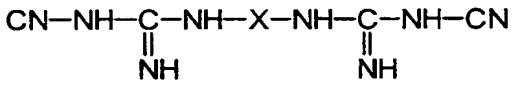
9. An antimicrobial polymer according to claim 8 wherein the polymeric biguanide is a mixture of poly(hexamethylenebiguanide) polymer chains in which the individual polymer chains, excluding the terminal groups, are represented by Formula (5) and salts thereof:



Formula (5)

wherein the value of n is from 4 to 40.

10. An antimicrobial polymer according to any one of claims 1 to 5 obtainable by co-polymerising a chromophoric marker, a bisdicyandiamide having the formula:

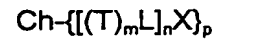


and a diamine H_2N-Y-NH_2, wherein X and Y are as defined in claim 8.

11. An antimicrobial polymer according to claim 10 obtainable by co-polymerising hexamethylenediamine, hexamethylene-1,6-bis dicyandiamide and a chromophoric marker.

12. An antimicrobial polymer according to any one of the preceding claims wherein the covalent bond between the chromophoric marker and polymer is formed by means of one or more reactive functional group on the chromophoric marker which is capable of forming a covalent bond with the polymer and/or monomer precursors used to make the polymer.

13. An antimicrobial polymer according to claim 12 wherein the chromophoric marker carrying the reactive functional group(s) is of the Formula (1):



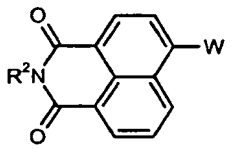
Formula (1)

wherein:

Ch	is a chromophoric group;
L	is a divalent aliphatic linking group;
X	is a reactive functional group;

	T	is -O-, -S-, -NR^1-, -$NR^1C(O)NR^1$-, -$NR^1C(S)NR^1$-, -$NR^1C(O)$-, -OC(O), =N- or -SO_2NR^1-;
	R^1	is H, optionally substituted alkyl or optionally substituted phenyl;
	m and n	independently are 0 or 1; and
	p	is 1 or 2.

14. An antimicrobial polymer according to claim 13 wherein the chromophoric marker carrying the reactive functional group(s) is of the Formula (2):



Formula (2)

wherein:

W is -NR^3R^4, -OR^5 or halogen;

R^2, R^3 and R^5 are each, independently, alkyl optionally substituted by a reactive functional group;

R^4 is H or alkyl optionally substituted by a reactive functional group;

provided that at least one of R^2 R^3 R^4 or R^5 is substituted by a reactive functional group.

15. An antimicrobial polymer according to claim 14 wherein the chromophoric marker carrying the reactive functional group(s) is N-(6-aminohexyl)-4-(6-aminohexylamino)-1,8-naphthalimide, N-(6-aminohexyl)-4-methoxy-1,8-naphalthimide, N-(6-aminohexyl)-4-bromo-1,8-naphalthimide or N-hexyl-4-(6-aminohexyl)-1,8-naphthalimide.

16. An antimicrobial polymer according to claim 10 obtainable by co-polymerising hexamethylenediamine, hexamethylene-1,6-bis dicyandiamide and 4-bromo-1,8-naphthalic anhydride.

17. A compound of the Formula (2) as defined in claim 14.

18. A composition comprising antimicrobial polymers at least one of which is an antimicrobial polymer according to any one of claims 1 to 16.

19. A composition comprising a carrier and an antimicrobial polymer according any one of claims 1 to 16 or a composition according to claim 18.

20. A method for inhibiting microbiological growth on, or in, a medium which comprises treating the medium with an antimicrobial polymer according to any one of claims 1 to 16 or a composition according to claim 18 or claim 19.

21. A method for detecting an antimicrobial polymer according to any one of claims 1 to 18 on or in a medium comprising the steps:

(a) subjecting a sample of the medium containing an antimicrobial polymer to a detection means whereby the presence of the chromophoric marker in the antimicrobial polymer generates a detection signal; and optionally

(b) calculating the concentration of the antimicrobial polymer from the detection signal generated in step (a).

22. A method according to claim 21 wherein the detection means comprises fluorescence spectrometry, Raman spectrometry or surface enhanced resonance Raman spectrometry.

23. A method for maintaining the concentration of an antimicrobial polymer according to any one of claims 1 to 18 in a medium at or above a target concentration comprising the steps:

(a) measuring the concentration of the antimicrobial polymer in the medium using the method according to claim 21 or claim 22;

(b) comparing the measured concentration with the target concentration; and

(c) adding a sufficient quantity of further antimicrobial polymer to the medium to maintain the concentration of the antimicrobial polymer in the medium at or above the target concentration.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02864

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N47/44 A01N33/12 C09B57/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01N C09B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	DATABASE WPI Section Ch, Week 197924 Derwent Publications Ltd., London, GB; Class A14, AN 1979-45362B XP002151861 & SU 619 489 A (AS USSR MICROMUL CP), 4 July 1978 (1978-07-04) abstract	1,3-5, 12,18,20
X	WO 98 02492 A (NALCO CHEMICAL CO) 22 January 1998 (1998-01-22) page 1, paragraph 1 page 2, paragraph 2 -page 3, paragraph 2	1-6,12, 18-23

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
2 November 2000	16/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lamers, W

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INTERNATIONAL SEARCH REPORT

Inte[redacted] Application No
PCT/GB 00/02864

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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X	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; S.C.CHANG ET AL.: "4-Alkylamino-3-bromo-N-alkyl-1,8-naphthal imides: new photochemically activatible antiviral compounds" retrieved from STN-INTRNATIONAL, accession no. 1994:244616 XP002151860 abstract "IT" & BIOORG. MED. CHEM. LETT., vol. 3, no. 4, 1993, pages 555-556,	17
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[redacted] Application No
PCT/GB 00/02864

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